

REMARKS

Claim 7 has been cancelled. Claims 1, 4-5, and 9-11 have been amended. New claim 12 is added. Claims 1-6 and 8-12 are now pending in this application. Support for the amendments is found in the existing claims and the specification as discussed below. Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Objection of Claims under 37 C.F.R. § 1.175(c)

Claims 10-11 were objected under 37 C.F.R. § 1.175(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. In particular, claims 10 and 11 failed to further limit the vaccine composition and the kit. Claims 10 and 11 are amended to be in independent form, placing them in compliance with 37 C.F.R. § 1.175(c).

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1-11 were rejected under 35 U.S.C. § 112, first paragraph as not being enabled by the Specification. In particular, the Examiner states on the one hand that the present vaccine composition is enabled for:

- (a) a polynucleotide vaccine component being vaccine Hepatitis B surface (HBs) antigen,
- (b) a protein antigen vaccine component being BSA, hen egg lysozyme or HBs antigen, and
- (c) a mineral based, negatively charged adjuvant.

On the other hand, the Examiner asserts that the present vaccine composition is not enabled for

- (a) any polynucleotide vaccine component;
- (b) any protein antigen vaccine component; and
- (c) a mineral based, negatively charged adjuvant.

The Applicants wish to point out that the Examiner is not correct regarding (a), in that also an enhanced activity has been shown for HBc Antigen (see e.g., Figure 1, page 7, lines 4-5 and page 8, line 20). The Applicants emphasize that a key aspect of the invention resides in the possibility to prepare combination vaccines consisting of two components: (1) a DNA

oligonucleotide component and (2) a specific mineral-based adjuvant adsorbed protein antigen. This permits predetermining a Th1-biased immune response (CMI) induction against one component in the vaccine and a Th2-biased immune response induction against the other component of the vaccine. Furthermore, the Applicants emphasize that the Th1 response will be directed towards the vaccine component that is encoded by the DNA oligonucleotide, whereas the Th2 response will be directed towards the protein antigen. In previous combined vaccine formulations containing mineral aluminium-based adjuvants the immune response induced towards all antigens present in the vaccine formulation was clearly Th2 biased.

As detailed in the application, it was not deemed possible previously to combine the DNA oligonucleotide component including its advantageous properties with the mineral-based adjuvant adsorbed protein antigen component with its advantageous properties. The Applicants are unaware of evidence in the public domain that it had been done previously by others.

The present inventors have now shown in the examples that the use of the mineral based, negatively charged adjuvant is critical for these combination vaccines.

With regard to the requirements of 35 USC 112, the detailed examples must not be read in isolation, but must be read in the context of the remainder of the description, which provides a good deal of detailed information on the techniques of the invention. Specifically, on page 6, lines 17-23 the method in general and the enhanced effect is described of preincubating or mixing said mineral-based negatively charged adjuvant with said protein antigen vaccine component prior to formulating with said polynucleotide vaccine component. In addition, on page 7, line 22-33, the *modus operandi* is provided of mineral-based, negatively charged adjuvants versus other adjuvants in respect of DNA. The experimental results substantiate the proposed *modus operandi*, and provide the necessary basis for the present scope of the claims. Seen in this light, it is submitted that the person skilled in the art can really derive the subject matter of the claims from the disclosure of the specification. Indeed, once in possession of the protocol, the skilled person would apply known and routine techniques to carry out the method. Since the constituent methods are known and well practiced, the skilled person would not encounter undue burden in order to monitor the event of interest according to the invention. Should guidance be necessary, the specification provides examples thereto on page 9, line 8 to page 13, line 8.

Since the specification makes sufficient disclosures illustrated with examples in respect of the polynucleotide vaccine components, the protein antigen vaccine component, and the mineral based, negatively charged adjuvant, it is evident that the specification teaches the skilled person how to carry out the invention.

The scope of protection sought by the Applicants is in keeping with the disclosure of an invention that is a broad principle applicable to many different situations. As stated in the abstract, the invention is useful for formulating combined DNA/protein antigen vaccine compositions in which the immunogenicity of the DNA vaccine component is effectively enhanced. Thus, from the specification there can be no doubt that the invention has a broad applicability. Since the application is directed towards a principle that can be generally applied, the claim language reflects the generality of the invention. For an invention such as the present general principle, the Applicant submits that it would not be possible to provide embodiments and examples for every envisaged instance of the DNA and protein vaccine component. However, provided in the application are variations of the invention across much of the scope of the claims. It should be noted that these variations still fall within the instructions provided for performing the general principle of the invention.

Since the present application is sufficiently clear and complete for the skilled person to be able to carry it out by way of examples and embodiments, and since the invention is directed towards a principle that is applicable to many situations, and the Applicant has provided in the specification several embodiments and instances together with generally applicable examples of the invention, the scope of the claims is commensurate with the invention, so the claims fulfill the requirements of 35 USC §112 first paragraph. On the other hand, limiting the claims would unjustifiably jeopardize the rights of the Applicant vis-à-vis its contribution to the state of the art.

The examiner asserts that "merely generating an immune response does not equate to providing protective immunity" (page 5 paragraph 2). Thus, it appears that the Examiner expects that a vaccine would necessarily protect from future infections. Furthermore, the Examiner requests "challenge" experiments. However, the interpretation by the Examiner is not correct. The term "vaccine" does not equate to providing protective immunity as a strict prerequisite, although this may be considered a desired goal for prophylactic vaccines. First of all, there are alternative types of vaccines, including therapeutic vaccines which are not meant to protect from

future infections, but could be targeted against e.g. cancer. Secondly, a formulation may be known as a "vaccine", if only it helps the body generating an immune response, e.g. raising antibodies or cell-mediated immunity. The following internet survey demonstrates common interpretations of the term "vaccine".

1. "A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. A vaccine can help the body recognize and destroy cancer cells or microorganisms. Cancer.govPatient" (cited from http://www.uccc.info/CancerCenter/content/CancerInfo/Details_g.asp?Id=CDR0000045938&Type=Glossary)

2. "Preparation containing immune-stimulating agents that is administered to trigger an immune response against a specific disease or infection" (cited from <http://www.antigenics.com/glossary/definition.phtml?word=239>).

3. "immunogen consisting of a suspension of weakened or dead pathogenic cells injected in order to stimulate the production of antibodies [syn: vaccinum] (cited from WordNet (r) 2.0)

4. "<pharmacology> A suspension of attenuated or killed microorganisms (bacteria, viruses or rickettsiae), administered for the prevention, amelioration or treatment of infectious diseases." (cited from <http://www.books.md/V/dic/vaccine.php>)(<http://www.biology-online.org/dictionary/Vaccine>)

In the present invention, the term "vaccine" is well-defined on page 5. In particular, a "DNA vaccine" or "polynucleotide vaccine" is only designated a vaccine once it "has been shown to express that respective antigen". In addition, a "vaccine protein antigen" is only designated a vaccine once it "refers to an antigen". Per definition, an antigen elicits an immune response. We further understand that the applicant may be his or her own lexicographer.

Moreover, as mentioned above, the contribution of the present invention resides in the use of the mineral based, negatively charged adjuvant, which is crucial for these combination vaccines. Previously, it was not possible to design a combination vaccine so as to obtain a predetermined differential immune response consisting of specific Th1 and Th2 immunity. The

present invention demonstrates for the first time the feasibility of this approach of pre-incubating or mixing the phosphate-containing negatively charged mineral adjuvant, as exemplified by aluminium phosphate gel adjuvant with the protein antigen, prior to the addition of the DNA component.

Thus, the claims relate to vaccines, i.e., components which have been demonstrated previously to act as an antigen. However, now these different components, known for its function, can be formulated together.

Finally, the cited art is not applicable. Specifically, the Examiner states that "the art indicates that it would require undue experimentation to formulate and use successful **attenuated live or whole cell vaccine** without the prior demonstration of vaccine efficacy." (emphasis added). Thus, the present compositions relate to a protein component as such and polynucleotide components as such, but not to cells. Moreover, the applicants point out that adjuvants are normally not used in attenuated live vaccines at all.

In view of Applicants' arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 1-11 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention.

Referring to part a) of the rejection, Claim 1 recited "said formulation" without sufficient antecedent basis. Claim 1 is amended by substituting the phrase with "said polynucleotide vaccine component".

Referring to part b), Claims 4 and 5 were rejected because acronyms like IEP and HBV must be spelled out when used for the first time in a chain of claims. Claims 4 and 5 are amended to correct these deficiencies.

Referring to part c), claim 5 was rendered indefinite because claim includes elements not actually disclosed (those encompassed by the "i.e."). Claim 5 is amended by substituting "i.e." with "a".

Referring to part d), limitations of claim 5 were not cited in the alternative. Claim 5 is amended to cite the limitations in the alternative by substituting the term "and" with "and/or".

The Applicants note that the vaccine compositions comprise at least one protein antigen.

Referring to part e, claim 9 was considered to be indefinite because it recited a process without reciting any active, positive steps. Claim 9 is amended to recite the steps of preincubating or subsequently mixing the mineral-based, negatively charged adjuvant with said at least one protein antigen vaccine component prior to being formulated with said polynucleotide vaccine component. Thus, the claims are in compliance with 35 U.S.C. § 112, second paragraph.

In view of Applicants' amendments and comments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 101

Claim 9 was rejected under 35 U.S.C. § 101 was rejected because it recited a use without setting forth any steps involved in the process. As indicated above, Claim 9 is amended to recite the steps of preincubating or subsequently mixing the mineral-based, negatively charged adjuvant with said at least one protein antigen vaccine component prior to being formulated with said polynucleotide vaccine component. Thus, the claims are in compliance with 35 U.S.C. § 101.

In view of Applicants' amendment, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 102(b)

Claims 1-11 were rejected under 35 U.S.C. § 102(b) as being anticipated by Dalemans et al., (WO 99/30733).

However, Dalemans et al. provides a very general list on adjuvants, without specifying a preference for mineral-based negatively charged adjuvants. On this basis alone, the present invention is novel over Dalemans et al. Moreover, Dalemans et al. does not provide any order of mixing the components, let alone preincubating or mixing said mineral-based negatively charged adjuvant with a protein antigen vaccine component prior to formulating with a polynucleotide vaccine component as required by the present invention. As a consequence, the product obtained by following the method of Dalemans et al. differs from the product according to the present invention.

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The Applicants have amended claim 1 to incorporate the feature: "... wherein said mineral-based negatively charged adjuvant is preincubated or subsequently mixed with said at least one protein antigen vaccine component prior to formulating with said polynucleotide vaccine component." As a result of this feature, the structure of the vaccine composition in toto differs from the prior art vaccine formulations. This formulation results in a significantly enhanced immunogenicity of the polynucleotide vaccine component, as extensively described in the application. Methods to demonstrate the efficacy or immunogenicity of a vaccine belong to the common general knowledge. In addition, the present invention provides tests to demonstrate the immunogenicity of a given vaccine. Accordingly, the presently claimed subject matter is novel over Dalemans et al. and withdrawal of the rejection is respectfully requested.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

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Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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